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In re Patent Application of:
Satishchandra P. Patel

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For: PHARMACEUTICAL COMPOSITIONS Examiner: Not Yet Assigned

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
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Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
United Kingdom	0218004.0	August 2, 2002

In support of this claim, a certified copy of the said original foreign application is filed herewith.

Dated: April 20, 2004

Respectfully submitted,

By Edward A. Meilman

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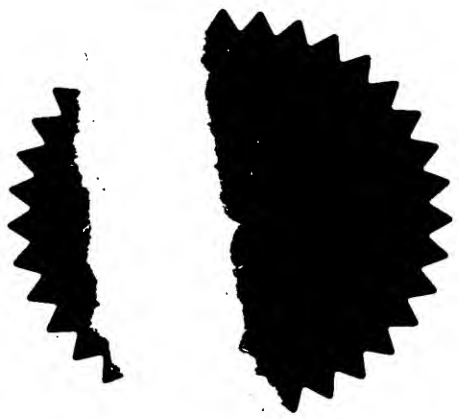

Signed R. Mahoney

Dated 8 April 2004

Form 1/77

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3 Full name, address and postcode of the or of each applicant (underline all surnames)

Patel, Satishchandra Punambhai
27 Yale Court
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0218004.0

Patents ADP number (if you know it)

8438194 001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention Pharmaceutical Compositions

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

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8. Is a statement of inventorship and of right to grant of a patent required in support ofthis request? (Answer 'Yes' if: NO
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11. I/We request the grant of a patent on the basis of this application.

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GB Patent Filings
0207 400 3000

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Document : 777686

Pharmaceutical Compositions

The present invention relates to pharmaceutical compositions, in particular a micro-emulsion concentrate for cyclosporins.

The cyclosporins are a class of cyclic undecapeptides, with important pharmacological activities, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activities. The first of the cyclosporins to be isolated, and the most commonly known cyclosporin, is Cyclosporin A, formulations of which are commercially available under the trade marks SANDIMMUNE (RTM) and NEORAL (RTM).

The cyclosporins are very lipophilic and hydrophobic compounds, which are sparingly soluble in water, but dissolve readily in organic solvents such as methanol, ethanol, chloroform and the like. The low solubility in water results in extremely low bioavailability of the cyclosporins when administered orally. This may lead to higher dosages being required, with the consequent possibility of undesirable side effects. Therefore, to provide an effective therapeutic concentration of the drug in the body when administered orally represents a considerable challenge. Extensive research has been conducted to find cyclosporin formulations that are effective for oral administration. There are a number of preparations of cyclosporins suitable for oral administration proposed by the prior art.

Prior art formulations of cyclosporins for oral administration have often involved combinations of the cyclosporin with a surfactant, an oil, and a co-surfactant. Such formulations have been intended to be diluted with water prior to drinking. However, this is rather inconvenient, and also the resulting aqueous composition has an unpleasant taste.

In order to alleviate the problems of having to dilute the composition with water prior to oral administration, and the unpleasant taste of the resulting solution, liquid

compositions have been formulated into soft capsule preparations. For example, the formulation commercially available under the trade mark SANDIMMUNE (RTM) is encapsulated in a soft capsule with a gelatine shell. The formulation contains ethanol in order to solubilise the cyclosporin. However, the ethanol can permeate the gelatine shell of the capsule and is volatile at room temperature. This means that the composition of the contents can vary during storage. If too much ethanol is lost, the cyclosporin may precipitate from the composition, with adverse effects on the bioavailability. This results in uncertainties about dosage.

US 4,388,307 discloses compositions comprising a cyclosporin together with at least one of the following components:

a) a trans-esterification product of a natural or hydrogenated vegetable oil triglyceride and a polyalkylene polyol;

b) a saturated fatty acid triglyceride; and

c) a mono- or di-glyceride.

It is preferred that ethanol be used as a further solubilising agent, and the compositions for oral administration disclosed in the Examples all contain ethanol.

US 5,342,625 discloses pharmaceutical compositions comprising cyclosporins in micro-emulsion pre-concentrate and micro-emulsion form. The compositions contain a cyclosporin disposed in a composition comprising a hydrophilic phase, a lipophilic phase and a surfactant. The hydrophilic phase comprises 1,2-propylene glycol or R_1-(O-(CH_2))$_x$-OR_2 wherein R_1 is a C_{1-5} alkyl or a tetrahydrofurfuryl group, R_2 is a C_{1-5} alkyl or a tetrahydrofurfuryl group or is hydrogen, and X is from 1 to 6. The lipophilic phase typically comprises a fatty acid triglyceride. The compositions may contain a C_{1-5} alkanol, such as ethanol, as a co-solvent. However, the compositions disclosed in US 5,342,625 include components which are restricted for pharmaceutical use by several regulatory agencies world-wide, including the FDA, because they are not considered "Generally Recognised As Safe" (GRAS) for oral use.

US 5,759,997 discloses pharmaceutical compositions comprising a cyclosporin, a fatty acid triglyceride, and a glycerol fatty acid partial ester or propylene glycol or sorbitol

complete or partial ester. The compositions may also comprise a viscosity reducer, such as the trans-esterification product of a natural vegetable oil triglyceride and a polyalkylene polyol. Ethanol can also be used, but is less preferred. The compositions may also comprise an emulsifying agent, preferably a tenside having a hydrophilic-lipophilic balance (HLB) of at least 10.

US 6,057,289 discloses pharmaceutical compositions comprising cyclosporin and a carrier comprising

(a) a cyclosporin solubilising agent consisting essentially of C_6 to C_{22} fatty acids; and

(b) a water-soluble non-ionic surfactant.

The surfactant should have a hydrophilic-lipophilic balance (HLB) greater than 10, and suitable surfactants include polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives and the like. The compositions are for forming microemulsions upon contact with an aqueous medium.

US 5,858,401 discloses compositions that comprise a cyclosporin, a medium chain monoglyceride of C_6 to C_{12} fatty acids, having a monoglyceride content of at least 50%, and at least one surfactant. The surfactant may be, for example, polyglycolised glycerides or ethoxylated glycerides having a molecular weight of PEG between 400 and 2000 and a fatty acid chain length between C_6 to C_{18}. The compositions are for forming microemulsions upon contact with an aqueous medium.

Having regard to the state of the art, it is clear that it is desirable to provide further formulations of cyclosporins suitable for oral administration, and in particular ones which can be formulated in capsules such as soft gelatine capsules, and which are emulsion concentrates (that is, homogeneous solutions which on exposure to water or gastrointestinal fluids form an emulsion having a particle size of less than 5 microns), and preferably microemulsion concentrates, which avoid the use of volatile components

such as ethanol, and which utilise compounds which are Generally Recognised As Safe (GRAS).

There is also a continued need to provide cyclosporin formulations for oral administration which can have high cyclosporin concentrations (thereby reducing the size of capsule required for a given dosage), which exhibit high oral bioavailability, and which are stable (in particular stable against precipitation of the cyclosporin) upon storage. It is also desirable that formulations should have as few components as possible, thereby resulting in ease of manufacture.

The present invention aims to provide cyclosporin compositions which, at least to some extent, satisfy these requirements.

According to the present invention, there is provided a pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns, the solution comprising:

(a) a pharmaceutically effective amount of a cyclosporin,

(b) a carrier medium comprising a triglycerol monoester of a fatty acid having from 6 to 30 carbon atoms or mixtures thereof,

(c) polyethylene glycol,

(d) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10, and

(e) optionally, a viscosity reducing agent.

The present invention is partly based upon the discovery that the carrier medium as defined in (b) above represents a particularly good solvent medium for cyclosporins, and therefore it is possible to avoid co-solvents such as ethanol, propylene glycol, or the

like. The compositions according to the present invention accordingly preferably do not have such co-solvents, and in particular preferably do not contain ethanol.

The compositions according to the present invention preferably do not contain appreciable amounts of water, that is, they are substantially water-free.

The compositions according to the present invention exhibit excellent stability upon storage, and high concentrations of cyclosporins in the compositions can be achieved.

The compositions according to the present invention are homogeneous mixtures which exhibit excellent bioavailability of the cyclosporin *in vivo*.

The cyclosporin is preferably Cyclosporin A. The cyclosporin preferably makes up from 1 to 25% by weight of the composition, more preferably makes up from 5 to 20% by weight of the composition, and most preferably makes up from 10 to 20% by weight of the composition. The cyclosporin is present in the composition of the present invention in pharmaceutically effective amounts. These amounts are well-known in the art. For example, when treating chronic inflammations or provoking an immunosuppressive effect, it is preferred that the daily dose ranges from about 3 mg/kg to about 50 mg/kg.

The carrier medium comprises a triglycerol monoester of a fatty acid having from 6 to 30 carbon atoms, preferably from 8 to 18 carbon atoms, or mixtures thereof. Preferred compounds for the carrier medium are the triglycerol monoesters of capric acid, caprylic acid, lauric acid, oleic acid, or mixtures thereof. Triglycerol monooleate is particularly preferred.

The carrier medium preferably makes up from 15 to 50% by weight of the composition, more preferably from 20 to 40% by weight, and most preferably 25 to 35% by weight of the composition.

The non-ionic surfactant preferably makes up from 5 to 40% by weight of the composition, more preferably makes up from 10 to 30% by weight of the composition, and most preferably makes up from 15 to 25% by weight of the composition.

The Hydrophilic Lipophilic Balance (HLB) of the non-ionic surfactant is greater than 10, more preferably greater than 12 and most preferably greater than 14.

The non-ionic surfactant must be capable of forming a stable emulsion, preferably a fine emulsion (particle size less than 1 micron), and more preferably a microemulsion, of the composition when it is brought into contact with aqueous fluid, such as in the G.I. tract.

The non-ionic surfactant is preferably selected from the group consisting of: polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils, polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, and polyoxyethylene castor oil derivatives. Particularly preferred surfactants are set out in **Table 1**. Mixtures of these surfactants can also be used.

Trade Name	**Description**
TWEEN (RTM) 20	Polyoxyethylene (20) sorbitan monolaurate
TWEEN (RTM) 40	Polyoxyethylene (20) sorbitan monopalmitate
TWEEN (RTM) 60	Polyoxyethylene (20) sorbitan monostearate
TWEEN (RTM) 80	Polyoxyethylene (20) sorbitan monooleate
NIKKOL (RTM) HCO30	PEG-30 hydrogenated castor oil
NIKKOL (RTM) HCO40	PEG-40 hydrogenated castor oil
NIKKOL (RTM) HCO50	PEG-50 hydrogenated castor oil
NIKKOL (RTM) HCO60	PEG-60 hydrogenated castor oil
CREMOPHORE (RTM) RH40	Polyoxyethylene 40 castor oil
CREMOPHORE (RTM) RH60	Polyoxyethylene 60 castor oil
CREMOPHORE (RTM) EL35	Polyoxyethylene 35 castor oil

Table 1

The compositions according to the present invention contain polyethylene glycol (also known as carbowax) as a co-solvent for the cyclosporin. The polyethylene glycol preferably has a molecular weight of from 200 to 1000, more preferably from 200 to 600. The polyethylene glycol preferably makes up from 5 to 40% by weight, more

preferably from 10 to 35% by weight, and most preferably makes up from 20 to 30% by weight of the composition.

Polyethylene glycol can affect the integrity of gelatin capsules, rendering the shell walls brittle, particularly in the case of hard gelatin capsules. However, in compositions according to present invention, this problem can be mitigated by ensuring that the proportion of the carrier medium, surfactant, and viscosity reducing agent, taken together, is higher than the proportion of polyethylene glycol in the composition (i.e. the weight ratio of the carrier medium, surfactant and viscosity reducing agent taken together to polyethylene glycol is greater than 1.0).

The compositions according to the present invention may also contain a viscosity reducing agent. The viscosity reducing agent may be added if the formulation is otherwise too viscous, and any compound is suitable provided that it is not toxic by oral administration and suitably lowers the viscosity of the composition. Suitable agents are monoesters of glycerol and aliphatic monocarboxylic acids having from 6 to 30 carbon atoms, preferably from 8 to 18 carbon atoms, or mixtures thereof. Particularly preferred viscosity reducing agents are glycerol monocaprylate and glycerol monooleate. The viscosity reducing agent, when present, preferably makes up from 5 to 25%, more preferably 10 to 20%, by weight of the composition.

The pharmaceutical compositions according to the present invention may further comprise an antioxidant. This antioxidant, when present, is preferably present in an amount of from 0.01% to 2% by weight of the composition, and more preferably from 0.5 to 1% by weight of the composition. The antioxidant may be any suitable antioxidant, such as are well known to those skilled in the art. Particularly preferred antioxidants are butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), and alpha-tocopherol.

Other additives, excipients, and diluents normally used in the pharmaceutical arts may optionally be added to the composition. These include thickening agents, dispersing agents, flavouring agents, sweetening agents, colouring agents, stabilising agents

(including pH stabilisers), and preservatives. However, the compositions of the present invention preferably consist only of the components defined in Claim 1, or at least comprise at least 90%, more preferably at least 95%, and more preferably at least 98% by weight of the components defined in Claim 1.

The pharmaceutical compositions according to the present invention may be formulated as a drinking solution, or as a hard or soft capsule. Soft capsule formulations are particularly preferred. Gelatine capsules are also preferred.

The pharmaceutical compositions according to the present invention can be conveniently prepared by uniformly and thoroughly mixing the carrier medium, the cyclosporin, and the surfactant together at room temperature or at slightly elevated temperature, such as a temperature up to 40°C, until a clear solution is obtained, and then cooling the composition to room temperature. The other additives indicated above are then thoroughly admixed therewith. The cyclosporin remains in solution and does not crystallise or precipitate out.

Compositions according to the present invention are preferably for administration to mammals, and especially to humans. It is preferred that the pharmaceutical compositions of the present invention are administered in capsule, liquid-oral, drink solution, or the like form. In a preferred embodiment, the composition is in a form adapted for oral administration in oral unit dosage form. Capsules, e.g., soft or hard gelatine capsules, which represent the preferred oral dosage form, are specially suitable unit dosage forms for oral administration.

Oral unit dosage forms in accordance with the present invention will suitably comprise from 5 to 400 mg and more preferably from 20 to 200 mg, e.g., 25, 50, 100, 125, 150, or 200 mg of cyclosporin. The dosage of the drug and the number of times administered to the patient will vary depending on several factors such as: the age of the patient, the severity of the condition of the patient, and past medical history, and will be a matter to be determined by the attending physician.

When the composition of the present invention is prepared in the form of a soft or hard capsule, the composition may be encapsulated in a gelatine shell which contains any conventional plasticizer. Suitable plasticizers are: glycerine, sorbitol, hexanetriol propylene carbonate, hexane glycol, sorbitans, tetrahydrofuryl alcohol ether, diethylene glycol monoethyl ether, 1,3-trimethyl-2-imidazolidone, dimethylisosorbide, and mixtures of these. However, the plasticizer is not limited to those just mentioned, and any suitable plasticizer can be used.

Encapsulation can be achieved by standard techniques which are well known in the art.

Compositions according to the present invention exhibit high solubility of cyclosporin, thereby reducing the size of the capsule or other oral unit dosage form. They also employ only materials that are GRAS for oral use.

The invention will now be further described with reference to the following Examples, it being understood that these are intended to illustrate the invention, and in no way to limit its scope.

Examples

The examples used the ingredients and in the amounts indicated in **Table 2**. Cyclosporin A was dissolved in the carrier medium, the other components were added, and the mixture was mixed for from 10 to 30 minutes at room temperature until the solution was homogeneous.

The solution was then stored overnight up to 24 hours to ensure that no crystallisation occurred.

The verify that an emulsion was formed, one part of each composition was added to 10 parts of water and stirred gently. There was formed a fine emulsion having a particle size of less than 5 microns, and the Cyclosporin A did not precipitate or crystallise out.

The composition is suitable for encapsulation into a hard or soft gelatine capsule.

Ingredients	Example 1	Example 2	Example 3
	weight/mg	weight/mg	weight/mg
Cyclosporin A	100	25	100
Triglycerol monooleate (CAPROL (RTM) 3GO)	200	100	200
Polyethylene glycol 400	200	65	200
Glycerol mono caprylate (CAPMUL (RTM) MCM)	120	30	
Glycerol mono oleate (CAPMUL (RTM) GMO)			120
Polyoxyethylene 35 castor oil (CREMOPHORE (RTM) EL)	150	-	150
Polyoxyethylene sorbitan mono laurate (TWEEN (RTM) 20)		75	
Alpha tocopherol	5	5	5
Total	775mg	300mg	775mg

Table 2

Comparative Example

The composition according to Example 1 was compared with the analogous example (Comparative Example 1) which was identical to Example 1 except that the triglycerol monooleate was replaced with hexaglycerol dioleate. These solutions were maintained at room temperature for four weeks and compared for their physical stability.

Ingredients	Example 1	Comparative Example 1
	weight/mg	weight/mg
Cyclosporin A	100	100
Triglycerol monooleate (CAPROL (RTM) 3GO)	200	-
Hexaglycerol dioleate (CAPROL (RTM) 6G20)	-	200
Polyethylene glycol 400	200	200
Polyoxyethylene 35 castor oil (CREMOPHORE (RTM) EL)	150	150
Glycerol mono caprylate (CAPMUL (RTM) MCM)	120	120
Alpha tocopherol	5	5
Total	775mg	775mg

Table 3

The results are shown in Table 4.

Conditions	Example 1	Comparative Example 1
	Observation	
Initial	Clear solution	Clear/hazy solution
4 weeks at 25°C	Clear solution	Hazy suspension with crystals

Table 4

CLAIMS

1. A pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns, the solution comprising:

   (a) a pharmaceutically effective amount of a cyclosporin,

   (b) a carrier medium comprising a triglycerol monoester of a fatty acid having from 6 to 30 carbon atoms or mixtures thereof,

   (c) polyethylene glycol,

   (d) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10, and

   (e) optionally, a viscosity reducing agent.

2. A pharmaceutical composition according to Claim 1, wherein the carrier medium comprises a triglycerol monoester of capric acid, caprylic acid, lauric acid, oleic acid, or a mixture thereof.

3. A pharmaceutical composition according to Claim 2, wherein the carrier medium comprises triglycerol monooleate.

4. A pharmaceutical composition according to any of Claims 1 to 3, wherein the cyclosporin makes up from 1 to 25% by weight of the composition.

5. A pharmaceutical composition according to Claim 4 wherein the cyclosporin makes up from 5 to 20% by weight of the composition.

6. A pharmaceutical composition according to any of Claims 1 to 5, wherein the carrier medium makes up from 20 to 50% by weight of the composition.

7. A pharmaceutical composition according to Claim 6, wherein the carrier medium makes up from 25 to 35% by weight of the composition.

8. A pharmaceutical composition according to any of Claims 1 to 7, wherein the non-ionic surfactant makes up from 5 to 40% by weight of the composition.

9. A pharmaceutical composition according to Claim 8, wherein the non-ionic surfactant makes up from 15 to 25% by weight of the composition.

10. A pharmaceutical composition according to any of Claims 1 to 9, wherein polyethylene glycol makes up from 5 to 40% by weight of the composition.

11. A composition according to any of Claims 1 to 10, wherein the polyethylene glycol has a molecular weight of from 200 to 1000.

12. A pharmaceutical composition according to any of Claims 1 to 11, wherein the non-ionic surfactant is selected from the group consisting of: polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils, polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, and polyoxyethylene castor oil derivatives.

13. A pharmaceutical composition according to Claim 12, wherein the non-ionic surfactant is selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, PEG-30 hydrogenated castor oil, PEG-40 hydrogenated castor oil, PEG-50 hydrogenated castor oil, PEG-60 hydrogenated castor oil, polyoxyethylene 40 castor oil, polyoxyethylene 60 castor oil, polyoxyethylene 35 castor oil, and mixtures thereof.

14. A pharmaceutical composition according to any of Claims 1 to 13, wherein a viscosity reducing agent is present and makes up from 5 to 25% by weight of the composition.

15. A pharmaceutical composition according to any of Claims 1 to 14, wherein a viscosity reducing agent is present and selected from the group consisting of monoesters of glycerol and aliphatic monocarboxylic acids having from 6 to 30 carbon atoms, preferably from 8 to 18 carbon atoms, and mixtures thereof.

16. A pharmaceutical composition according to Claim 15, wherein a viscosity reducing agent is present and selected from the group consisting of glycerol monocaprylate, glycerol monooleate, and mixtures thereof.

17. A pharmaceutical composition according to any of Claims 1 to 16, comprising an antioxidant.

18. A pharmaceutical composition according to Claim 17, wherein the antioxidant is present in an amount of from 0.01% to 2% by weight of the total composition.

19. A pharmaceutical composition according to Claim 17 or Claim 18, wherein the antioxidant is selected from the group consisting of BHA, BHT, and alpha-tocopherol.

20. A pharmaceutical composition according to any of Claims 1 to 19, wherein the cyclosporin is Cyclosporin A.

21. A pharmaceutical composition according to any of Claims 1 to 20, formulated as a drinking solution.

22. A pharmaceutical composition according to any of Claims 1 to 20, formulated as a hard or soft capsule.

23. A composition according to any of claims 1 to 22, wherein the weight ratio of the carrier medium, non-ionic surfactant and viscosity reducing agent taken together to polyethylene glycol is greater than 1.0.

ABSTRACT

Pharmaceutical Compositions

The application discloses pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns, the solution comprising:

(a) a pharmaceutically effective amount of a cyclosporin, in particular Cyclosporin A

(b) a carrier medium comprising a triglycerol monoester of a fatty acid having from 6 to 30 carbon atoms or mixtures thereof,

(c) polyethylene glycol,

(d) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10, and

(e) optionally, a viscosity reducing agent.

The preferred carrier medium is triglycerol monooleate. Examples of the viscosity reducing agent are glycerol monocaprylate and glycerol monooleate.